Impact of age, tumor characteristics, and treatment on local control and disease outcome in early stage breat cancer : an EORTC translational research project

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CHAPTER 11

Summary

In *Chapter 1*, a general introduction and an outline of the present thesis are given.

In *Chapter 2*, the eleven year follow up results of EORTC study 10854 are presented, comparing one short intensive course of polychemotherapy (fluorouracil, doxorubicin, cyclophosphamide; FAC) to no peri-operative chemotherapy in 2795 stage I en II breast cancer patients, randomized between 1986 and 1991. Peri-operative chemotherapy was associated with significant better progression free survival rates (59% vs 53% without peri-operative chemotherapy) and locoregional control rates (91% vs 86%) respectively. In the subgroup of patients that did not receive prolonged systemic chemotherapy, one course of peri-operative chemotherapy led to significant higher overall survival rates as well (HR=0.80; 95% CI: 0.64–0.98; P = 0.035).

In *Chapter 3*, the five-year results of EORTC study 10902 are presented, comparing neoadjuvant anthracyclin based polychemotherapy versus the same chemo-therapeutic regimen given postoperatively. EORTC trial 10902 randomized 698 patients between 1991 and 1999. No significant differences between the two treatment arms were observed for progression-free and overall survival. Overall survival after 5 years was 82% in the preoperative group and 84% in the postoperative group (HR 1.16; 95% CI: 0.83 to 1.63; P = 0.38). Progression-free survival rates after 5 years for the preoperative and postoperative groups were 65% and 70%, respectively (HR 1.15; 95% CI, 0.89 to 1.48; P = 0.27). Time to locoregional recurrence was not significantly different between the two treatment arms (HR 1.13; 95% CI, 0.70 to 1.81; P = 0 .61).

In *Chapter 4*, the predictive role of p53 expression is studied in patients receiving neoadjuvant chemotherapy. Using tumor response as a surrogate endpoint, associations between p53 expression as well as other tumor markers like Her2 and outcome were studied. Tumor biopsy specimens were taken from 107 patients prior to the administration of neoadjuvant chemotherapy. In a multivariate logistic regression analysis, pCR was independently predicted by *p53* overexpression estimated by immunohistochemistry (OR 16.83; 95% CI, 1.78 to 159.33; P = 0.01) and negative pathological lymph node status (OR 8.47; 95% CI, 0.88 to 81.82; P = 0.07). In multi-variate Cox regression analysis, positive pathological lymph node status and no use of tamoxifen showed unfavourable prognosis for overall and distant disease-free survival.

In *Chapter 5,* the potential prognostic impact of a putative tumor marker called PS6K on locoregional recurrence is presented. The PS6K protein is encoded by the RPS6KB1 gene is located at chromosome and amplified in approximately 10% of all primary breast cancer cases. PS6K is a protein that is involved in the cell cyclus. It is rapidly activated in response to mitogenic stimuli, for example growth factors, cytokines, and oncogene products. In a series of 452 node-negative premenopausal early-stage breast cancer patients PS6K overexpression was associated both with worse distant disease-free survival and with impaired locoregional control (HR 1.80, P = 0.025 and HR 2.50, P = 0.006, respectively). In a multivariate analysis including other prognostic factors, PS6K overexpression remained an independent predictor for poor locoregional control (RR 2.67, P = 0.003). Therefore, PS6K could be a putative predictive and prognostic factor to be used in the planning of less or more aggressive locoregional therapy.

In *Chapter 6*, a retrospective analysis is presented concerning the impact of loco-regional treatment on disease outcome. Breast-conserving surgery and mastectomy with or without radiotherapy to the axilla and / or breast are compared in terms of locoregional control and disease outcome. The combined data set consisted of 3648 patients. 5.9% of the patients who were treated with mastectomy and 10.8% of the patients who were treated with breast-conserving therapy had a locoregional recurrence ($P < 0.0001$). The risk of death after breast-conserving therapy was similar compared with mastectomy (RR 1.07, $P = 0.37$). Adjuvant radiotherapy after mastectomy was associated with a lower risk for locoregional recurrence (RR 0.43, $P < 0.001$) and death (RR 0.73, $P = 0.001$). The effect of adjuvant radiotherapy after mastectomy was most profound in patients who had 1–3 positive nodes (RR 0.48, 99% CI 0.31–0.75, $P < 0.001$).

In *Chapter 7*, risk factors for locoregional recurrence and the relationship between locoregional recurrence and subsequent metastatic disease are studied in more detail. To that end, different time intervals between locoregional recurrence and subsequent metastatic disease are defined and compared in sensitivity analyses. The study population comprised 3602 women who had undergone primary surgery for early stage breast cancer. The results of multivariate analysis showed that younger age and breast conservation were risk factors for isolated loco-regional recurrence; breast cancer under 35 years of age versus over 50 years of age: HR 2.80 (95% CI 1.41 to 5.60); breast cancer age 35–50 years versus over 50 years: HR 1.72 (95% CI 1.17 to 2.54); breast conservation: HR 1.82 (95% CI 1.17 to 2.86). After perioperative chemotherapy, less isolated loco-regional recurrences were observed (HR 0.63; 95% CI 0.44 to 0.91).
Therefore we hypothesised that, assuming an isolated loco-regional recurrence to be a potentially curable condition, women treated with breast conservation or diagnosed with breast cancer at a young age should be monitored closely to detect local recurrence at an early stage.

In *Chapter 8*, a translational research project is presented concerning very young breast cancer patients. The total dataset consisted of 9938 early breast cancer patients. Tumor material was collected from 549 patients aged under 41 years of age at time of diagnosis. In the multivariate analyses, only histological grade remained a significant prognostic factor for both overall survival (Grade II HR 2.67; 95% CI 0.91 to 7.80; $P = 0.07$, Grade III HR 3.92; 95%CI 1.38 to 11.16; $P = 0.01$) and distant metastasis free survival (Grade II HR 2.04; 95% CI 1.07 to 3.88; $P = 0.03$, Grade III HR 2.38; 95%CI 1.29 to 4.39; $P < 0.01$). However, large tumor size remained an independent unfavorable prognostic factor on outcome in terms of distant metastasis free survival as well (HR 1.64 (1.17-2.31) $P < 0.01$). In the subgroup of node negative very young breast cancer patients, histological grade remained an independent prognostic factor for both overall survival (Gr III HR 8.92; 95%CI 1.17 to 68.20; $P = 0.04$) and distant disease-free survival respectively (Gr III HR 4.12; 95%CI 1.42 to 11.98; $P < 0.001$).

In *Chapter 9*, the efficacy of chemotherapy in early breast cancer is studied according to hormone receptor status in patients aged less than 41 years. The median follow up period was 7.3 years. Patients that received chemotherapy did not have significant

differences in overall survival (HR 0.87, P = 0.63) and distant metastasis-free survival (HR 1.36, P = 0.23) rates according to ER status. Patients with estrogen receptor (ER) positive tumors who did not receive adjuvant chemotherapy had better overall survival (HR 0.41, P < 0.01) and distant metastasis-free survival (HR 0.59, P = 0.02) rates than those with ER-negative tumors. Therefore, it was concluded that very young early stage breast cancer patients with ER-positive tumors benefit less from adjuvant systemic chemotherapy than patients with ER-negative tumors. Similar results were demonstrated for progesterone receptor status.

In *Chapter 10*, the results of this thesis are discussed within the scope of current breast cancer therapy and research. Finally, suggestions are made concerning future directions in translational and clinical breast cancer research.